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## GeneAssist™ Pathway Atlas

### Mechanism of Botulinum Toxin Overview

Botulinum neurotoxin (BoNT) is one of the most potent toxins that inhibit neurotransmitter release at the neuromuscular junction. It is a microbial product synthesized by an anaerobic, gram-positive, spore-forming bacterium *Clostridium botulinum* whose strains include *C. botulinum*, unique strains of *Clostridium baratii* and *Clostridium butyricum* also have the capacity to produce the potent neurotoxin. BoNT is enzymatic. The toxin is a zinc-dependent protease that cleaves one or more proteins by which neuronal vesicles release ACh (Acetylcholine) into the neuromuscular junction. This toxin acts pre-synaptically to block ACh release and is both an agent that causes disease (i.e., botulism) as well as an agent to treat the disease (e.g., dystonia). The ability of BoNT to produce its effects is largely dependent on its ability to pierce intracellular membranes. Thus, the toxin that is ingested or inhaled can bind to epithelial cells and be transported to the cytosol (Ref. 1).

There are 3 main clinical forms of botulism: food borne, intestinal and wound related. Food borne botulism occurs when the preformed BoNT is eaten. Intestinal botulism occurs when spores are ingested and reproduce in the gastrointestinal tract, releasing the toxin in situ (primary infection, secondary intoxication). Wound-related botulism occurs when anaerobic abscess allow germination of *C. botulinum* spores. Most of these cases originate in wounds contaminated with soil or intravenous drug users. Regardless of how the toxin gets into the gut, it must reach the general circulation for its full effect to manifest. Since the toxin is too large to pass through epithelial barriers by diffusion, it is actively transported through processes by which this occurs involves receptor-mediated transcytosis that does not damage the gastrointestinal tract and produces all seven known serotypes of the BoNT (A, B, C, D, E, F and G), whereas *C. baratii* and *C. butyricum* serotype each (F and E, respectively). Each type is antigenically distinct with its own characteristics. BoNTs are secreted as polypeptide chains of about 150 kDa each, which are cleaved endogenously or exogenously resulting into a 100 kDa heavy chain linked through a disulfide bond (Ref. 2). The botulinum toxin's mode of action involves three steps: extracellular translocation, membrane translocation and intracellular substrate cleavage, and blockage of ACh release. The heavy chain is responsible for the intracellular toxic activity. When the toxin reaches peripheral cholinergic nerve endings, it is followed by endocytosis and pH-induced translocation across the endosome membrane. The receptor for BoNT at the neuromuscular junction has been unequivocally identified. However, a sialic acid-containing molecule, and possibly a ganglioside, is implicated in its binding to the exact role played by this molecule. Once inside the low-pH endosome, the light chain dissociates and is released into the cytosol, where it acts as a zinc metalloprotease and cleaves SNARE (Soluble NSF-attachment protein) proteins. Without functional SNARE complexes, the neurotransmitter ACh is not released into the neuromuscular junction. Blockade of transmitter release accounts for flaccid paralysis and autonomic dysfunction that is characteristic of botulism. Although the toxin acts preferentially on cholinergic nerve endings, it does have the ability to block nerve endings as well. BoNT types A and E act on SNAP25 (Synaptosomal-associated protein of 25 kDa); serotypes B and D act on VAMP (Vesicle-Associated Membrane Protein), also known as synaptobrevin, and serotype C acts mainly on Syntaxin, cleaving SNAP25 (Ref. 1). By disrupting neurotransmission at cholinergic junctions in the autonomic nervous system, the various forms of botulism cause autonomic dysfunction. Its most life-threatening potential, however, is its ability to stop respiration by blocking neurotransmission in diaphragm and intercostal muscles.

Patients with botulism typically present with difficulty seeing, speaking, and/or swallowing. Prominent neurologic findings include diplopia, blurred vision, often enlarged or sluggishly reactive pupils, dysarthria, dysphagia, and dysphagia. The pharynx is injected because of peripheral parasympathetic cholinergic blockade. Sensory changes are infrequent. Circumoral and peripheral paresthesias from hyperventilation as a patient becomes frightened by onset of paralysis extend beyond bulbar musculature to loss of head control, hypotonia, and generalized weakness become prominent. Death results from airway obstruction (pharyngeal and upper airway muscle paralysis) and inadequate tidal volume and accessory respiratory muscle paralysis. Because botulism is intoxication, patients remain afebrile unless they have a secondary infection (e.g., aspiration pneumonia). The toxin does not penetrate brain parenchyma, however they often have communication difficulties because of bulbar palsies (Ref. 3). Complications, such as eyelid ptosis, have been attributed to

(commonly referred to as Botox). An "hourglass" deformity, which is the consequence of temporalis muscle atrophy, in addition to acting as a toxin during botulism infection, Botox is also now being used to treat several disorders. Careful small doses of the toxin is used to treat two eye muscle disorders - uncontrollable blinking (blepharospasm) and strabismus) and a neurological movement disorder that causes severe neck and shoulder contractions, known as cervical dystonia. Botox not only affects the neuromuscular junction directly but also have intrinsic pain controlling effects by acting on affecting pain perception. Recently Botox injection has come into vogue as a treatment for facial wrinkles. In the case of wrinkles, it was discovered that people who suffered from migraines had a decrease in the frequency and severity of headaches. Additional studies are necessary in order to validate the effects of BoNT in the treatment of migraines. In toxin has also proven to be a safe and effective therapy for a variety of somatic and autonomic motor disorders. Urol clinical success with urethral and bladder Botox injections in the treatment of detrusor-sphincter dyssynergia, non-ne-spasticity, and refractory overactive bladder (Ref.5). The main treatment for severe botulism is meticulous supportive include mechanical ventilation. To be most effective, the antitoxin must be given before much toxin has bound to prey in cases of wound-related botulism, the wound must be debrided and therapy with an appropriate antibiotic such as p Recovery takes weeks to months and occurs when new presynaptic end plates and neuromuscular junctions are formed used to reduce wrinkles and treat several disorders, BoNTs are also among the most lethal biological substances to h a highly toxic aerosol form. New vehicles for transmission have emerged in recent decades, and wound botulism asso heroin has increased dramatically since 1994. Such a potential bioterrorist threat necessitates the development of th countermeasures against BoNTs.

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